International Journal of Cardiology 223 (2016) 750–757

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Efficacy of alirocumab in high cardiovascular risk populations with or without heterozygous familial hypercholesterolemia: Pooled analysis of eight ODYSSEY Phase 3 clinical program trials

Michel Farnier [a,*], Daniel Gaudet [b], Velichka Valcheva [c], Pascal Minini [d], Kathryn Miller [e], Bertrand Cariou [f]

[a] Lipid Clinic, Point Médical, Dijon, France
[b] Lipidology Unit, Community Genomic Medicine Center, Department of Medicine, Université de Montréal and ECOGENE-21 Clinical and Translational Research Center, Chicoutimi, Quebec, Canada
[c] Global Medical Affairs, Sanofi, Paris, France
[d] Biostatistics and Programming, Sanofi, Chilly-Mazarin, France
[e] Biostatistics and Data Management, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[f] Department of Endocrinology, l'Institut du Thorax, Nantes University Hospital, Nantes, France

ARTICLE INFO

Article history:
Received 6 June 2016
Accepted 16 August 2016
Available online 18 August 2016

Keywords:
Alirocumab
Hypercholesterolemia
Low-density lipoprotein cholesterol

ABSTRACT

Objectives: Despite maximally tolerated statin therapy, many patients with high cardiovascular risk, with or without heterozygous familial hypercholesterolemia may require additional low-density lipoprotein cholesterol (LDL-C) reduction. We report pooled alirocumab (ALI) efficacy and safety data from eight Phase 3 trials in 4629 hypercholesterolemia patients, receiving background statin therapy.
Material and methods: Studies were pooled by ALI dose and control: ALI 75/150 mg every 2 weeks (Q2W; dose increased to 150 mg Q2W at Week 12 based on Week 8 LDL-C) versus ezetimibe (EZE; Pool 1) or placebo (PBO; Pool 2), and ALI 150 mg Q2W versus PBO (Pool 3).
Results: Mean baseline LDL-C was 109 vs. 105 mg/dL (Pool 1), 129 vs. 130 mg/dL (Pool 2) and 126 vs. 125 mg/dL (Pool 3). ALI 75/150 mg Q2W reduced LDL-C by 48.9% (vs. −19.3% EZE) and 48.6% (vs. +4.2% PBO) from baseline to Week 24, and ALI 150 mg Q2W reduced LDL-C by 60.4% (vs. +0.5% PBO; all $p < 0.0001$). LDL-C reductions were sustained to Week 104. Risk-based LDL-C goals (<70 mg/dL or <100 mg/dL) were achieved by 78.0%, 75.2%, and 79.0% (Pool 1–3) of ALI-treated patients (vs. 52.4%, 6.4%, and 8.4%, respectively, for controls) at Week 24. Consistent reductions were observed in apolipoprotein B, non-high-density lipoprotein cholesterol, and lipoprotein (a) ($p < 0.0001$ vs. control). Common adverse events in ALI-treated patients were nasopharyngitis, injection-site reactions, upper respiratory tract infections, and influenza.
Conclusions: Alirocumab treatment significantly reduced LDL-C in high cardiovascular risk patients, enabling most to achieve risk-based LDL-C goals.

1. Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for developing and worsening of atherosclerotic cardiovascular disease (ASCVD) [1]. LDL-C reduction is particularly important in people defined as having a high risk of CV events, including those with familial dyslipidemia, severe hypertension, diabetes mellitus, moderate chronic kidney disease (CKD) or a calculated SCORE risk of fatal CV disease of ≥5% [2,3]. However, many of these patients do not reach LDL-C targets, despite receiving maximally tolerated statin therapy [1,3,4].

Although LDL-C remains the primary focus of lipid-lowering therapy (LLT), other lipoproteins, such as non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (apo) B, are also recognized as important risk factors. In fact, it has been proposed that these may more accurately reflect the level of circulating atherogenic lipoprotein than LDL-C (calculated using the Friedewald equation) [4]. Lipoprotein(a) [Lp(a)] is an apo B-containing atherogenic lipoprotein that predicts CV risk and is associated with aortic valvular disease independently of LDL-C; it is recognized that statin therapy has little, if any, effect on this parameter.

Alirocumab (a monoclonal antibody that binds to and inhibits proprotein convertase subtilisin/kexin type 9, preventing low-density lipoprotein receptor degradation and thereby increasing LDL-C clearance) has been approved for the treatment of hypercholesterolemia in

Abbreviations: Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); Q2W, every 2 weeks; TEAE, treatment-emergent adverse event.

* Corresponding author at: Point Médical, Rond Point de la Nation, 21000 Dijon, France.
E-mail address: michelfarnier@nerim.net (M. Farnier).

http://dx.doi.org/10.1016/j.ijcard.2016.08.273
0167-5273/

the USA and the European Union as an adjunct to diet and maximally tolerated statin therapy [5,6]. In the USA, alirocumab is indicated for use in adults with HeFH or clinical ASCVD who require additional lowering of LDL-C [6]; in Europe, approval includes adults with primary hypercholesterolemia (HeFH and non-familial) or mixed dyslipidemia, with or without other LLTs, in patients unable to reach LDL-C goals with maximum tolerated statin. In Europe, the indication also specifically permits the use of alirocumab as monotherapy or combination therapy with other LLTs in statin-intolerant patients, or for those where statins are contraindicated [5].

Here, we present a pooled analysis of alirocumab efficacy and safety data from eight ODYSSEY Phase 3 clinical trials of up to 104 weeks in high-risk patients (including people with HeFH, and people with established CVD, or risk equivalents). Each trial was conducted in individuals on background statin therapy. In six of the eight studies, individuals received maximally tolerated statins (accounting for 91% of the total number of individuals included in the pooled dataset), while in the other two studies a fixed dose of background statin was used, either atorvastatin 20–40 mg or rosuvastatin 10–20 mg. In all the individual trials, alirocumab treatment at a dose of 75 or 150 mg every 2 weeks (Q2W) resulted in a significant reduction in LDL-C versus controls in patients at high CV risk with or without HeFH [7–13]. For the pooled analysis, we report on the effects of alirocumab treatment on LDL-C and other lipid parameters, including non-HDL-C, apo B, and Lp(a).

2. Methods

2.1. Study designs and pooling strategy

This analysis includes data from eight Phase 3 randomized, double-blind, controlled trials (Fig. 1). Methods of the individual trials have been reported previously [8,9,11–14]. Patients were randomized to either alirocumab or control in a 2:1 ratio (1:1 ratio in the OPTIONS I and II studies) and received double-blind study treatment for 24–104 weeks.

For the purposes of the present analysis, efficacy data were analyzed in three pools according to the alirocumab dose and control used in each individual trial. Three trials compared alirocumab 75/150 mg Q2W versus ezetimibe (Pool 1, n = 1130), three trials compared alirocumab 75/150 mg Q2W versus placebo (Pool 2, n = 1051), and two trials compared alirocumab 150 mg Q2W versus placebo (Pool 3, n = 2448) (Fig. 1). In Pools 1 and 2, the alirocumab dose was increased in a blinded fashion from 75 to 150 mg Q2W at Week 12 if Week 8 LDL-C level was ≥70 mg/dL (or ≥70 or ≥100 mg/dL, depending on CV risk, in the OPTIONS I and II studies). Safety data were analyzed in two pools according to control group.

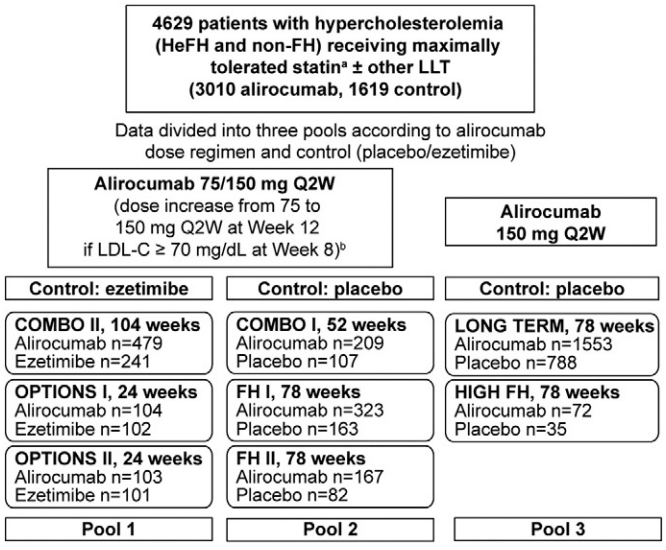

Fig. 1. Pooling strategy. For purposes of this analysis, efficacy data were analyzed in three pools according to alirocumab dose (75/150 mg or 150 mg Q2W) and control (ezetimibe or placebo). For safety analysis, Pool 2 and Pool 3 were combined. n values refer to the number of patients in the randomized study populations. [a] Maximally tolerated statin was defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. Fixed doses of atorvastatin 20–40 mg and rosuvastatin 10–20 mg were used in OPTIONS I and II, respectively. [b] In the OPTIONS studies, dose was increased if LDL-C was ≥70 mg/dL (prior CHD) or ≥100 mg/dL (CHD risk equivalents). CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolemia; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q2W, every 2 weeks. Clinicaltrials.gov identifiers: COMBO II, NCT01644188; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; FH I, NCT01623115; FH II, NCT01709500; COMBO I, NCT01644175; LONG TERM, NCT01507831; HIGH FH, NCT01617655.

2.2. Patients

The FH I, FH II, and HIGH FH studies exclusively recruited patients with HeFH and who were therefore at high CV risk. COMBO I and II recruited non-FH patients at high CV risk (established CHD/CVD or CHD risk equivalents [e.g. CKD or diabetes mellitus with other risk factors]). The other studies recruited both HeFH patients and non-FH patients at high CV risk (as above plus people without documented CHD or CVD but with a 10-year risk of fatal CVD ≥5% [SCORE] in the OPTIONS studies). For study entry, LDL-C at screening had to be ≥70 or 100 mg/dL, depending on CV risk (except in LONG TERM, where LDL-C was ≥70 mg/dL for all patients, and in HIGH FH, where LDL-C had to be ≥160 mg/dL). Eligibility also required all patients to be receiving maximally tolerated statin, with or without other LLT, which was continued throughout the study as background therapy. Exceptions were the OPTIONS I and II trials, which used fixed doses of atorvastatin 20–40 mg and rosuvastatin 10–20 mg, respectively, and COMBO II, in which no other LLT was allowed. Maximally tolerated statin was defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg (lower doses were allowed with an investigator-approved reason, e.g. intolerance). All studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and applicable amendments laid down by the World Medical Assemblies, and the International Conference Harmonization guidelines for Good Clinical Practice. For each participating study site, institutional review board or independent ethics committee approval of the protocols was ascertained and written informed consent was obtained from all patients.

2.3. Endpoints and statistical analysis

Efficacy endpoints included the percentage change in LDL-C (calculated using the Friedewald formula), apo B, non-HDL-C, Lp(a), triglycerides, HDL-C, and apo A1 from baseline to Week 12 (before possible dose increase) and Week 24 (primary endpoint in each individual study), and the proportion of patients achieving risk-based LDL-C goals. Data were analyzed using an intention-to-treat approach, including all lipid data regardless of adherence to treatment. An analysis using only on-treatment data was also performed. Least-squares mean lipid values were calculated from a mixed-effects model with repeated measures to account for missing data, as described previously [15]. Adjusted means were calculated for Lp(a) and triglycerides, with missing values calculated by multiple imputation followed by robust regression. Combined estimates were calculated for LDL-C goal achievement, with missing data accounted for by multiple imputation followed by logistic regression. Safety was assessed via reporting of treatment-emergent adverse events (TEAEs) and laboratory values. Adverse events were classed as TEAEs if they were reported from the first dose of study treatment up to the last dose plus 70 days. Descriptive statistics only were used for safety analyses (no formal statistics were planned in the study protocols).

3. Results

3.1. Patients

In total, this analysis included 4629 patients (1130 in Pool 1, 1051 in Pool 2, and 2448 in Pool 3). Demographic and baseline characteristics were similar for the alirocumab and control groups within the study pools (Table 1). More patients were male than female, and the majority of patients were white. A history of ASCVD was reported for the majority of patients; Pool 1, 84.5% alirocumab versus 79.5% control; Pool 2, 56.5% versus 56.8%; Pool 3, 75.0% versus 77.0%, and a history of diabetes was reported in 35.4% versus 37.4% in Pool 1, 18.9% versus 20.2% in Pool 2, and 34.7% versus 34.5% in Pool 3, respectively (Table 1). Pool 2 had the lowest proportion of patients with diabetes or ASCVD, and this pool had the highest baseline LDL-C values (Table 1). A greater proportion of patients in Pool 2 had HeFH (69.9%) as the FH I and FH II studies exclusively recruited patients with this condition (Table 1). Lower rates of ASCVD, diabetes and higher LDL-C are all reflections of the enrichment in FH patients. Most patients were receiving maximally tolerated statin therapy (91%). In Pool 1, 11% of alirocumab-treated individuals were also receiving additional LLT at study entry (vs. 12% control group) compared with 57% and 28% of alirocumab-treated individuals in Pools 2 and 3 (vs. 62% and 28% in respective control groups).

3.2. LDL-C reductions

The pooled alirocumab groups demonstrated significantly greater reductions from baseline in LDL-C at Weeks 12 and 24 versus ezetimibe or placebo (Fig. 2). At Week 12, before potential alirocumab dose increase in those studies utilizing the dose increase strategy, LDL-C was reduced with alirocumab 75 mg Q2W by 49.2% (vs. 22.3% with ezetimibe) in Pool 1 and 44.5% (vs. an increase of 4.1% with placebo) in Pool 2; the reduction with the 150 mg Q2W dose at Week 12 was 62.6% versus an increase of 1.1% with placebo in pool 3 (all comparisons $p < 0.0001$; Fig. 2A). For pools 1 and 2, dose increase to 150 mg Q2W at Week 12 occurred in 18% and 35% of patients, respectively. At Week 24, LDL-C was reduced with alirocumab 75/150 mg Q2W by 48.9% (vs. 19.3% with ezetimibe, Pool 1) and 48.6% (vs. a 4.2% increase with placebo, Pool 2), and was reduced with alirocumab 150 mg Q2W (Pool 3) by 60.4% (vs. a 0.5% increase with placebo, all comparisons $p < 0.0001$; Fig. 2B). LDL-C reductions with alirocumab were observed from Week 4 and were maintained up to 78/104 weeks (Fig. 3). Across the three pools, significantly more patients achieved their risk-based LDL-C goals with alirocumab (75–79% by Week 24) versus ezetimibe (52%) or placebo (6–8%) (Fig. 4).

3.3. Changes in other lipid parameters

In addition to the LDL-C reductions, levels of non-HDL-C, apo B, and Lp(a) were all significantly reduced with alirocumab (Fig. 5; $p < 0.0001$). Significant reductions in triglycerides were observed with alirocumab versus placebo in Pools 2 and 3 (10.3% and 17.0%, respectively, at Week 24; $p < 0.0001$; Table 2). Reductions in triglycerides versus ezetimibe were not significant (Table 2, Pool 1). HDL-C and apo A1 levels increased modestly but significantly ($p < 0.0001$) following alirocumab treatment versus placebo and versus ezetimibe (Table 2).

3.4. Safety summary

Overall rates of TEAEs, serious adverse events, deaths, and discontinuations were similar between alirocumab and control groups (Table 3). TEAEs occurring more frequently (≥5.0%) with alirocumab versus placebo were nasopharyngitis (12.6% vs. 12.1%), influenza (6.3% vs. 5.4%), diarrhea (5.3% vs. 4.9%), and injection site reaction (7.2% vs. 5.3%); those occurring more frequently with placebo versus alirocumab were upper respiratory tract infection (8.0% vs. 7.0%), back pain (6.0% vs. 5.3%), headache (5.5% vs. 5.1%), and arthralgia (6.5% vs. 5.1%). TEAEs with a higher incidence in the alirocumab versus ezetimibe groups were upper respiratory tract infection (7.7% vs. 6.8%), headache (5.0% vs. 3.6%), hypertension (5.5% vs. 5.2%), and injection site reaction (2.6% vs. 1.1%); those occurring with higher incidence in the ezetimibe versus alirocumab groups were nasopharyngitis (5.2% vs. 4.7%) and dizziness (5.4% vs. 4.8%). In alirocumab- and ezetimibe-treated patients, 0.3% and 0.2% permanently discontinued due to injection site reaction; corresponding numbers for alirocumab versus placebo were 0.2% and 0.3%.

4. Discussion

This pooled analysis included 4629 high CV risk patients from eight Phase 3 trials whose LDL-C levels were inadequately controlled despite maximally tolerated background statin with or without other LLTs. The majority of patients (73%) had a history of ASCVD, and a large proportion had HeFH (28.1%) or diabetes (31.5%). In this cohort of patients, the addition of alirocumab significantly reduced LDL-C levels versus ezetimibe or placebo controls (48.6–60.4% across the pools at Week 24, $p < 0.0001$ versus control), and LDL-C reductions were maintained for the duration of treatment, up to 104 weeks. Across all three pools, consistent significant reductions with alirocumab were also observed in atherogenic lipid parameters, non-HDL-C, apo B, and Lp(a), at Week 24. The alirocumab treatment effect on Lp(a) (17.4–25.1% reduction vs. control) contrasted with that of statin therapy, which appears to have had little or no effect on this parameter [16,17]. Modest reductions in triglycerides and increases in HDL and apo A1 were also seen in alirocumab-treated patients.

In six of the eight studies analyzed, individuals received maximally tolerated statins (accounting for 91% of the total number of individuals included in the pooled dataset). Overall, 58.4% of all participants were tolerant of high-dose statins (defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg) at study entry and as background therapy throughout the trial period; the remainder received lower doses (as per protocol with an investigator-approved reason, e.g. myalgia). However, baseline data demonstrated a need for further LLT, particularly for those individuals who did not achieve their LDL-C targets or who were unable to tolerate higher doses of statin therapy. In this high CV risk population, baseline mean LDL-C levels for all pools were >105 mg/dL, confirming the extent of the unmet need in these patients, despite statin therapy. Individuals in Pool 2 had the greatest unmet need, with the highest LDL-C levels at study entry (mean 129–130 mg/dL).

Studies in this pooled analysis were grouped by starting dose of alirocumab. Pools 1 and 2 had a lower starting dose of alirocumab (75 mg Q2W) than Pool 3 (alirocumab 150 mg Q2W). In Pools 1 and 2, Week 12 results gave an estimate of the efficacy of the two doses separately, before potential per-protocol dose increase. Significant reductions in LDL-C were observed from as early as 12 weeks; at this point, LDL-C was reduced by 44.5–49.2% from baseline with alirocumab 75 mg Q2W and by 62.6% with 150 mg Q2W. Improvements in other lipid parameters were also observed. At Week 12, the proportion of patients in the placebo-controlled pool who required a dose increase (35%) was higher than for the ezetimibe-controlled pool (18%). This is likely due to the higher proportion of HeFH patients having higher mean baseline LDL-C levels in the placebo-controlled pool.

The benefit of having two starting alirocumab doses is that it allows for flexibility and individualization of therapy based on each patient's LDL-C levels and treatment goals. For example, for those with inadequately controlled LDL-C levels (e.g. ≥160 mg/dL in the HIGH FH study) it may be appropriate to initiate treatment with 150 mg alirocumab Q2W, while those with lower LDL-C levels can be started on a lower dose of 75 mg Q2W, with the potential to increase the dose to 150 mg Q2W if goals are not met.

The pooled alirocumab efficacy data presented is consistent with that observed in other patient populations. Previously, alirocumab has significantly reduced LDL-C levels in studies performed without background statin (45% reduction with alirocumab [n = 126] versus 15% with ezetimibe [n = 125] in the ALTERNATIVE trial [18], and 47% [n = 52] versus 16% [n = 51], respectively, in the MONO trial [15]). In addition, overall safety data from the present pooled analysis demonstrated similar tolerability compared with the control groups and previous studies. The increased incidence of injection site reactions is considered to be related to alirocumab treatment, although most events reported have been rated as mild in severity and self-rate limiting [5,6]. The percentage of alirocumab-treated patients discontinuing due to injection site reactions was very low (≤0.3%).

Statin therapy, with or without other LLT, can reduce the risk of CV disease in high-risk patients, but tolerability and compliance issues may contribute to many patients failing to achieve desired LDL-C levels [19]. In other large scale trials, such as IMPROVE-IT (conducted in patients following acute coronary syndrome), lowering of LDL-C levels by approximately 24% was shown to significantly improve CV outcomes, and reductions below target levels conferred additional benefits [20]. In earlier studies using intensive statin therapy such as PROVE-IT [21] and TNT [22], LDL-C levels of 62 mg/dL and 77 mg/dL, were achieved with 80 mg atorvastatin. In the present analysis where alirocumab was added to the existing statin regimen (±other LLT), mean LDL-C levels of below the 70 mg/dL were achieved across all pools (Week 24, Pool 1, 54 mg/dL; Pool 2, 65 mg/dL; Pool 3,

Table 1
Baseline characteristics of randomized patients by analysis pool.

	Pool 1 Alirocumab 75/150 mg Q2W versus ezetimibe (n = 1130)		Pool 2 Alirocumab 75/150 mg Q2W versus placebo (n = 1051)		Pool 3 Alirocumab 150 mg Q2W versus placebo (n = 2448)	
	Alirocumab (n = 686)	Ezetimibe (n = 444)	Alirocumab (n = 699)	Placebo (n = 352)	Alirocumab (n = 1625)	Placebo (n = 823)
Age, years, mean (SD)	61.6 (9.7)	62.3 (9.7)	55.6 (12.9)	55.5 (12.5)	60.0 (10. 8)	60.2 (10.6)
Males, n (%)	483 (70.4)	294 (66.2)	397 (56.8)	216 (61.4)	1018 (62.6)	496 (60.3)
Race, white, n (%)	582 (84.8)	385 (86.7)	634 (90.7)	312 (88.6)	1505 (92.6)	760 (92.3)
BMI, kg/m^2, mean (SD)	30.3 (5.9)	30.7 (5.6)	30.0 (5.5)	30.1 (6.0)	30.1 (5.7)	30.5 (5.4)
HeFH, n (%)	26 (3.8)	18 (4.1)	490 (70.1)	245 (69.6)	348 (21.4)	174 (21.1)
Diabetes, n (%)	243 (35.4)	166 (37.4)	132 (18.9)	71 (20.2)	564 (34.7)	284 (34.5)
Cardiovascular disease history						
ASCVD, n (%)	580 (84.5)	353 (79.5)	395 (56.5)	200 (56.8)	1219 (75.0)	634 (77.0)
CHD, n (%)	547 (79.7)	336 (75.7)	368 (52.6)	192 (54.5)	1086 (66.8)	574 (69.7)
ACS, n (%)	401 (58.5)	241 (54.3)	245 (35.1)	134 (38.1)	734 (45.2)	394 (47.9)
Coronary revascularization procedure, n (%)	410 (59.8)	253 (57.0)	281 (40.2)	140 (39.8)	724 (44.6)	382 (46.4)
Other clinically significant CHD, n (%)	265 (38.6)	176 (39.6)	152 (21.7)	79 (22.4)	465 (28.6)	243 (29.5)
PAD, n (%)	32 (4.7)	16 (3.6)	17 (2.4)	13 (3.7)	80 (4.9)	43 (5.2)
Ischemic stroke, n (%)	55 (8.0)	31 (7.0)	39 (5.6)	10 (2.8)	160 (9.8)	76 (9.2)
Background therapy, n (%)						
Use of any statin	685 (99.9)	444 (100.0)	698 (99.9)	352 (100.0)	1624 (99.9)	822 (99.9)
High-dose statin[a]	328 (68.5)	165 (68.5)	541 (77.4)	282 (80.1)	784 (48.2)	396 (48.1)
Non-statin LLT	74 (10.8)	54 (12.2)	395 (56.5)	217 (61.6)	453 (27.9)	233 (28.3)
Baseline lipid parameters, mg/dL						
Calculated LDL-C, mean (SD)	109.4 (35.6)	105.0 (36.2)	129.0 (47.3)	130.3 (45.4)	125.9 (45.9)	125.3 (44.5)
Non-HDL-C, mean (SD)	139.3 (39.7)	135.4 (41.8)	155.5 (50.0)	155.8 (48.4)	155.8 (49.4)	155.4 (48.6)
Apo B, mean (SD)	94.3 (23.0)	92.3 (23.5)	106.1 (29.3)	105.6 (27.8)	103.5 (28.9)	103.3 (28.8)
Lp(a), median (Q1:Q3)	26.0 (8.0:74.0)	24.0 (10.0:61.0)	29.0 (10.0:81.0)	26.0 (8.0:75.0)	22.2 (7.7:66.1)	21.5 (6.7:66.8)
Triglycerides, median (Q1:Q3)	129.0 (96.0:185.0)	134.0 (97.0:187.0)	114.0 (85:161)	111.0 (86:156)	132.0 (94:182)	134.5 (95:189)
HDL-C, mean (SD)	48.0 (13.2)	48.3 (13.2)	50.5 (15.4)	49.7 (14.4)	49.8 (12.3)	49.8 (12.4)
Apo A1, mean (SD)	142.1 (23.8)	142.7 (24.7)	143.8 (27.3)	142.5 (27.1)	146.2 (25.1)	146.7 (27.2)

ACS, acute coronary syndrome (includes silent MI, acute MI, and unstable angina); Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); MI, myocardial infarction; PAD, peripheral artery disease; Q2W, every 2 weeks; SD, standard deviation.
[a] High-dose statin = atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. Pool 1: COMBO II, OPTIONS I, and OPTIONS II; Pool 2: COMBO I, FH I, and FH II; Pool 3: LONG TERM and HIGH FH.

51 mg/dL). The alirocumab studies included in this analysis were not designed to prospectively analyze occurrence of CV events, however, the effect of alirocumab on CV events is currently being assessed in the large-scale (n = 18,000 patients) ODYSSEY OUTCOMES trial (NCT01663402) [23].

5. Study limitations

The main limitation of this analysis is that it was a post hoc analysis of pooled studies and, as a result of pooling, the patient population covered a broad clinical spectrum, likely resulting in variations in

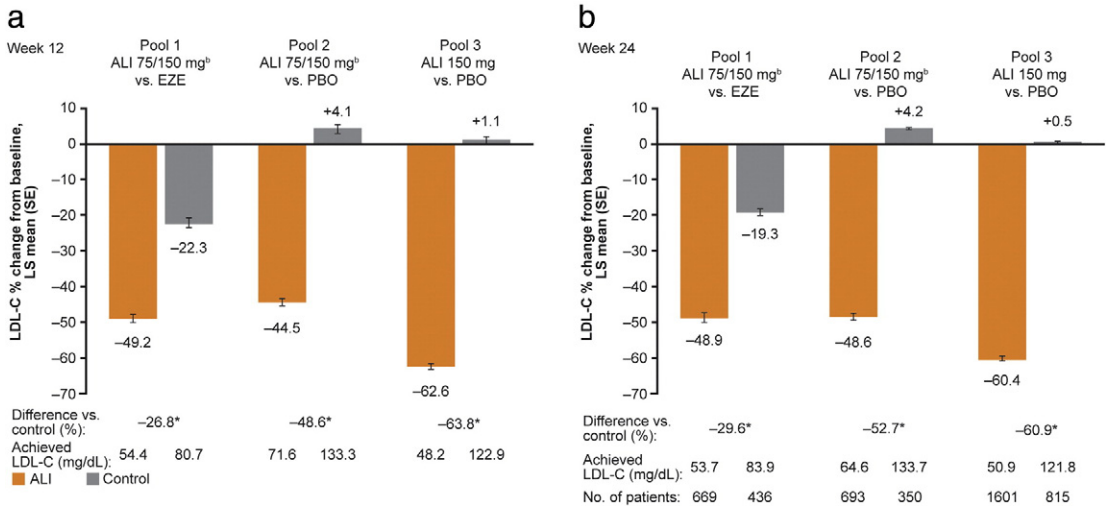

Fig. 2. LDL-C percentage reductions from baseline to Weeks 12 (a) and 24 (b)[a]. * $p < 0.0001$ vs. control. [a] Intention-to-treat analysis, including all lipid data collected regardless of adherence to treatment. [b] Dose increased from 75 to 150 mg Q2W at Week 12 in 18% and 35% of patients in the ezetimibe- and placebo-controlled pools, respectively. ALI, alirocumab; EZE, ezetimibe, LDL-C, low-density lipoprotein cholesterol; LS, least squares; PBO, placebo; Q2W, every 2 weeks; SE standard error.

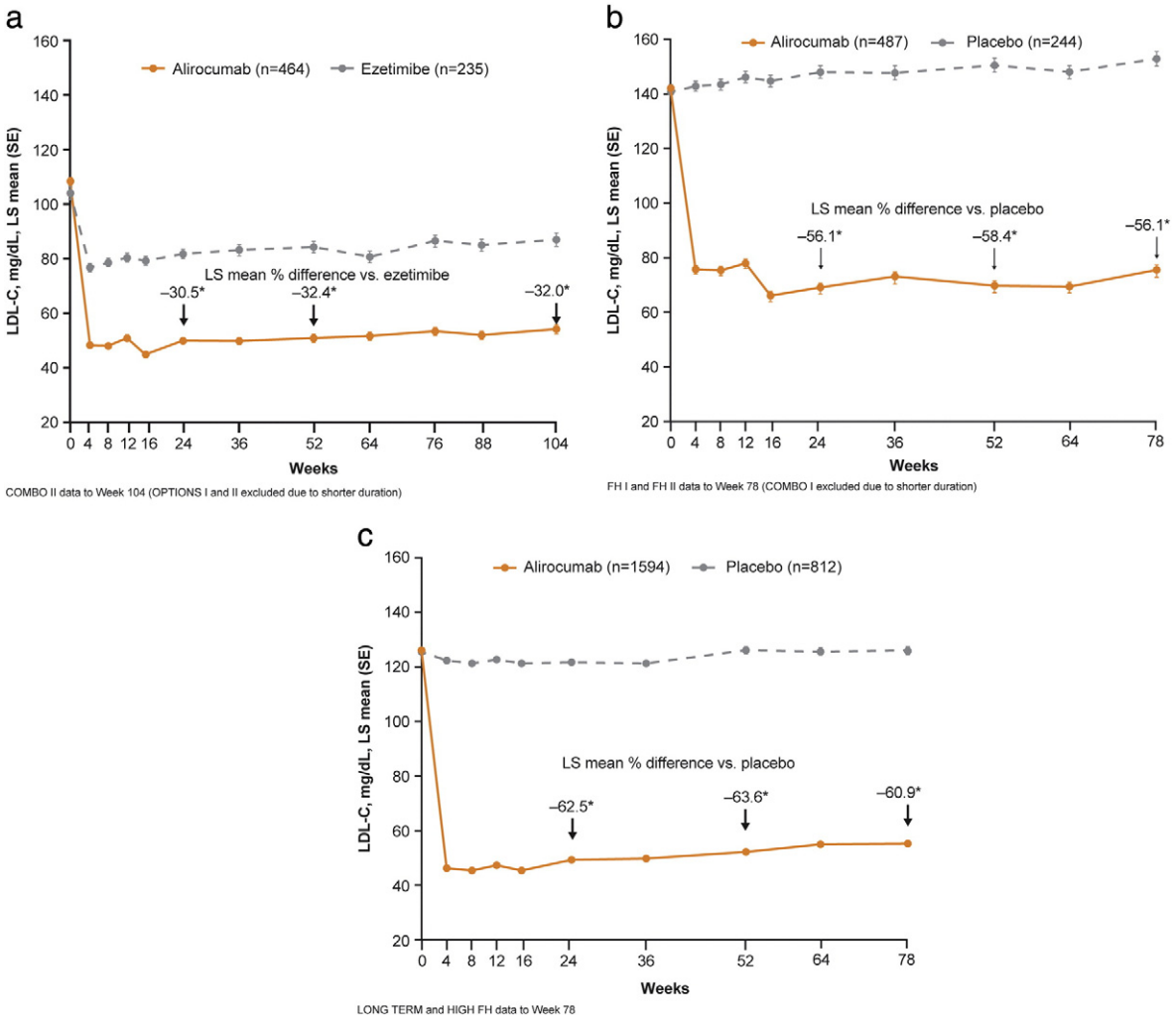

Fig. 3. LDL-C change over time (on-treatment population) (a) Pool 1; (b) Pool 2; (C) Pool 3.[a] * All p values <0.0001 vs. control. ([a]Pool 1 COMBO II to Week 104, OPTIONS I and OPTIONS II not included due to shorter duration (Week 24); Pool 2 FH I and FH II to Week 78, COMBO I not included due to shorter duration (52 weeks); Pool 3 LONG TERM and, HIGH FH, both studies shown to Week 78.). LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE standard error.

baseline characteristics. However, while data from an individual study provide information about a single study scenario, this pooled analysis of larger numbers of patients accumulated across the studies allows visualization of the data across different trial design elements (including patient population, dose regimen, control arm, and use of background LLTs). In addition to allowing further characterization of the data, the results also confirm the generalizability and consistency of the drug effect in less frequently represented subgroups in these studies.

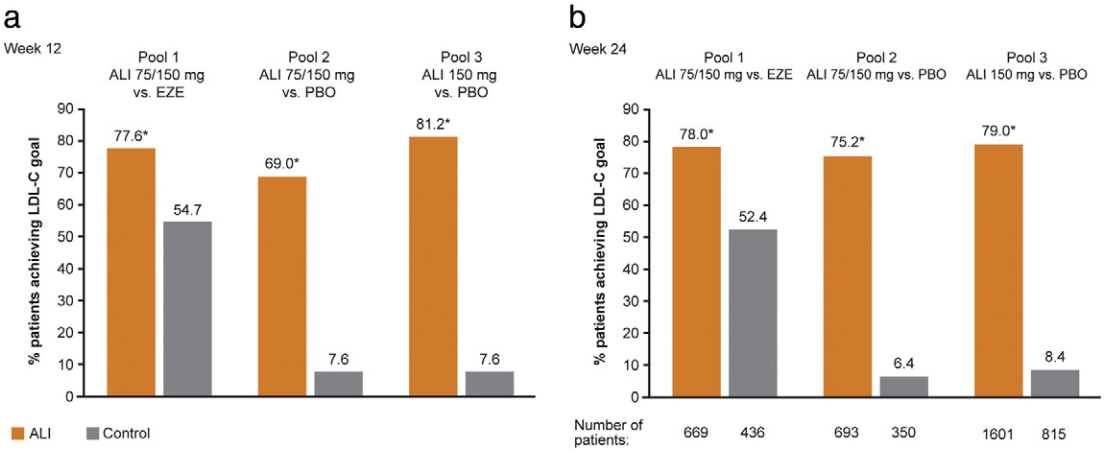

Fig. 4. Achievement of risk-based LDL-C goals[a] at Week 12 (a) and 24 (b)[b]. * p < 0.0001 vs. control. [a] LDL-C goals were <70 mg/dL for patients at very high CV risk, and <100 mg/dL for patients with high CV risk. Very high CV risk was defined as patients with CHD or CHD risk equivalents. High CV risk was defined as all other patients in these studies. [b] intention-to-treat analysis. ALI, alirocumab; CHD, coronary heart disease; CV, cardiovascular; EZE, ezetimibe, LDL-C, low-density lipoprotein cholesterol; PBO, placebo.

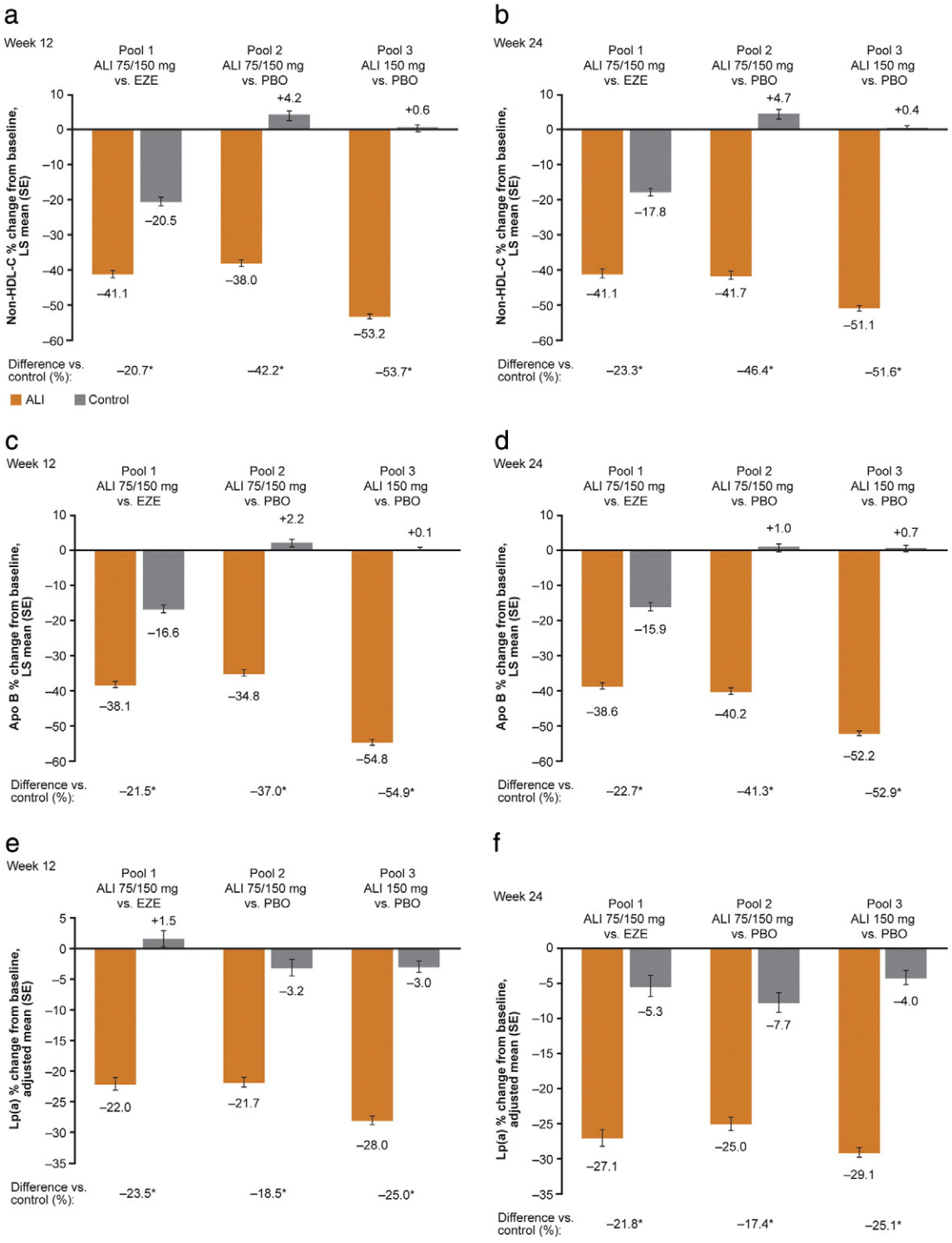

Fig. 5. Percentage changes in non-HDL-C, apo B, and Lp(a), at Week 12 (A, C, and E, respectively) and Week 24 (B, D, and F, respectively)[a]. * $p < 0.0001$ vs. control. [a] Intention-to-treat analysis. Apo, apolipoprotein; ALI, alirocumab; EZE, ezetimibe, HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LS, least squares; PBO, placebo; SE, standard.

6. Conclusions

In summary, in high CV risk patients on maximally-tolerated statin ± other LLT, alirocumab (75 or 150 mg Q2W) demonstrated significant LDL-C reductions versus controls, ranging from 47% to 60% according to study designs. Mean LDL-C levels below target levels of ≤70/≤100 mg/dL (dependent on CV risk) were achieved in all pools and significant improvements were seen in non-HDL-C, apo B, Lp(a), and other lipid parameters. Overall safety was comparable with controls, with a higher rate of injection site reactions with alirocumab.

Disclosures

Michel Farnier has received research support from/participated in speaker's bureau for Amgen, Merck, and Sanofi. He has received honoraria from Abbott, Eli Lilly, and Pfizer, and has been a consultant/on an

Table 2
Percentage changes in triglycerides, HDL-C, and apo A1 from baseline to Weeks 12 and 24.[a]

Values are mean (SE), %	Pool 1 Alirocumab 75/150 mg Q2W versus ezetimibe (n = 1130)		Pool 2 Alirocumab 75/150 mg Q2W versus placebo (n = 1051)		Pool 3 Alirocumab 150 mg Q2W versus placebo (n = 2448)	
	Alirocumab (n = 669)	Ezetimibe (n = 436)	Alirocumab (n = 693)	Placebo (n = 350)	Alirocumab (n = 1601)	Placebo (n = 815)
Triglycerides						
Week 12	−12.9 (1.0)	−12.8 (1.3)	−9.0 (1.1)	1.7 (1.5)	−16.4 (0.8)	0.9 (1.0)
Difference vs. control	−0.0[b]		−10.6[*]		−17.3[*]	
Week 24	−13.0 (1.2)	−11.2 (1.5)	–8.9 (1.1)	1.4 (1.5)	−15.3 (0.8)	1.7 (1.1)
Difference vs. control	−1.7[b]		−10.3[*]		−17.0[*]	
HDL-C						
Week 12	7.9 (0.6)	2.4 (0.7)	6.4 (0.6)	0.7 (0.8)	5.9 (0.4)	0.6 (0.5)
Difference vs. control	5.6[*]		5.7[*]		5.3[*]	
Week 24	8.1 (0.7)	0.8 (0.8)	6.6 (0.6)	−1.0 (0.8)	4.1 (0.4)	−0.4 (0.5)
Difference vs. control	7.4[*]		7.6[*]		4.5[*]	
Apo A1						
Week 12	3.4 (0.4)	−1.3 (0.6)	2.5 (0.5)	−0.9 (0.7)	4.6 (0.3)	0.6 (0.5)
Difference vs. control	4.7[*]		3.5[*]		3.9[*]	
Week 24	5.6 (0.5)	−0.6 (0.6)	4.0 (0.5)	−1.0 (0.7)	4.1 (0.4)	1.2 (0.5)
Difference vs. control	6.2[*]		5.0[*]		2.9[*]	

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; Q2W, every 2 weeks.
[*] $p < 0.0001$.
[a] Intention-to-treat analysis.
[b] Not significant.

advisory panel for Amgen, AstraZeneca, Roche, Kowa, Merck, Recordati, Sanofi, and Servier. Daniel Gaudet is a consultant/advisory panel member for Sanofi, Regeneron Pharmaceuticals, Inc., Amgen, Novartis, Ionis, Catabasis, Aegerion, Omthera, Uniqure, Chiesi, Gemphire, and Cymabay. Velichka Valcheva is an employee of and a stockholder in Sanofi. Pascal Minini is an employee of and a stockholder in Sanofi. Kathryn Miller is an employee of and a stockholder in Regeneron Pharmaceuticals, Inc.. Bertrand Cariou has received research funding from Sanofi, received honoraria from AstraZeneca, Pierre Fabre, Janssen, Eli-Lilly, MSD Merck & Co., Novo-Nordisk, Sanofi, and Takeda, and has acted as a consultant/advisory panel member for Amgen, DebioPharm, Genfit, Eli Lilly, Novo-Nordisk, Sanofi, and Regeneron Pharmaceuticals, Inc..

Contributions

Farnier M contributed to data analysis and interpretation, critical revision at all stages, and final approval.

Gaudet D contributed to data analysis and interpretation, critical revision at all stages, and final approval.

Valcheva V contributed to data analysis and interpretation, critical revision at all stages and final approval.

Minini P contributed to data analysis and interpretation, critical revision at all stages, and final approval.

Miller K contributed to data analysis and interpretation, critical revision at all stages, and final approval.

Cariou B contributed to data analysis and interpretation, critical revision at all stages, and final approval.

Acknowledgments

The authors would like to thank the following people for contributions to this manuscript: Desmond Thompson (Regeneron) and Guillaume Lecorps (Sanofi) for conducting data analyses, and Jaman Maroni, William J. Sasiela, Carol Hudson, and Richard Delgizzi (Regeneron) and Jay

Table 3
TEAEs (data pooled according to whether placebo or ezetimibe was used as control).

Values are n (%)	Ezetimibe-controlled pool[a]		Placebo-controlled pool[b]	
	Alirocumab (n = 686)	Ezetimibe (n = 443)	Alirocumab (n = 2318)	Placebo (n = 1174)
Patients with any TEAE	517 (75.4)	317 (71.6)	1851 (79.9)	954 (81.3)
Patients with any treatment-emergent SAE	134 (19.5)	75 (16.9)	385 (16.6)	202 (17.2)
Patients with any TEAE leading to death	6 (0.9)	9 (2.0)	16 (0.7)	13 (1.1)
Patients with any TEAE leading to permanent treatment discontinuation	56 (8.2)	31 (7.0)	144 (6.2)	67 (5.7)
TEAEs with incidence ≥5% patients in any group				
Nasopharyngitis	32 (4.7)	23 (5.2)	291 (12.6)	142 (12.1)
Upper respiratory tract infection	53 (7.7)	30 (6.8)	162 (7.0)	94 (8.0)
Influenza	29 (4.2)	18 (4.1)	147 (6.3)	63 (5.4)
Urinary tract infection	17 (2.5)	19 (4.3)	128 (5.5)	65 (5.5)
Headache	34 (5.0)	16 (3.6)	119 (5.1)	64 (5.5)
Dizziness	33 (4.8)	24 (5.4)	81 (3.5)	49 (4.2)
Hypertension	38 (5.5)	23 (5.2)	86 (3.7)	46 (3.9)
Diarrhea	18 (2.6)	13 (2.9)	123 (5.3)	57 (4.9)
Back pain	27 (3.9)	16 (3.6)	123 (5.3)	70 (6.0)
Arthralgia	32 (4.7)	15 (3.4)	118 (5.1)	76 (6.5)
Injection site reaction	18 (2.6)	5 (1.1)	167 (7.2)	62 (5.3)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a] Pool of COMBO II, OPTIONS I, and OPTIONS II studies.
[b] Pool of FH I, FH II, COMBO I, LONG TERM, and HIGH FH studies.

Edelberg, L. Veronica Lee, and Michael Howard (Sanofi) for providing critical review. Medical writing support was provided by Sarah Waite BSc (Hons) of Prime Medica Ltd, Knutsford, Cheshire, UK, funded by Sanofi and Regeneron Pharmaceuticals, Inc.. Responsibility for all opinions, conclusions, and interpretation of data lies with the authors.

This pooled analysis was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

References

[1] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, C.N. Bairey Merz, C.B. Blum, R.H. Eckel, et al., 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 63 (2014) 2889–2934.

[2] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. Heart J. 37 (2016) 2315–2382.

[3] Z. Reiner, A.L. Catapano, G. De Backer, I. Graham, M.R. Taskinen, O. Wiklund, et al., ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), Eur. Heart J. 32 (2011) 1769–1818.

[4] T.A. Jacobson, M.K. Ito, K.C. Maki, C.E. Orringer, H.E. Bays, P.H. Jones, et al., National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report, J. Clin. Lipidol. 9 (2015) 129–169.

[5] Sanofi-aventis. Praluent Summary of Product CharacteristicsAvailable at http://ec.europa.eu/health/documents/community-register/2015/20150923132812/anx_132812_en.pdf Accessed 17 December 2015.

[6] Sanofi-aventis U.S. LLC, Regeneron Pharmaceuticals Inc. Praluent™ Prescribing InformationAvailable at http://products.sanofi.us/praluent/praluent.pdf Accessed 17 December 2015.

[7] C.P. Cannon, B. Cariou, D. Blom, J.M. McKenney, C. Lorenzato, R. Pordy, et al., Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial, Eur. Heart J. 36 (2015) 1186–1194.

[8] H. Bays, D. Gaudet, R. Weiss, J.L. Ruiz, G.F. Watts, I. Gouni-Berthold, et al., Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial, J. Clin. Endocrinol. Metab. 100 (2015) 3140–3148.

[9] M. Farnier, P. Jones, R. Severance, M. Averna, E. Steinhagen-Thiessen, H.M. Colhoun, et al., Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial, Atherosclerosis 244 (2015) 138–146.

[10] H.N. Ginsberg, D.J. Rader, F.J. Raal, J.R. Guyton, C. Lorenzato, R. Pordy, et al., ODYSSEY HIGH FH: efficacy and safety of alirocumab in patients with severe heterozygous familial hypercholesterolemia, Circulation 130 (2014) 2119 Abstract.

[11] J.J. Kastelein, H.N. Ginsberg, G. Langslet, G.K. Hovingh, R. Ceska, R. Dufour, et al., ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia, Eur. Heart J. 36 (2015) 2996–3003.

[12] D.J. Kereiakes, J.G. Robinson, C.P. Cannon, C. Lorenzato, R. Pordy, U. Chaudhari, et al., Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study, Am. Heart J. 169 (2015) 906-15.e13.

[13] J.G. Robinson, M. Farnier, M. Krempf, J. Bergeron, G. Luc, M. Averna, et al., Efficacy and safety of alirocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1489–1499.

[14] J.J. Kastelein, J.G. Robinson, M. Farnier, M. Krempf, G. Langslet, C. Lorenzato, et al., Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies, Cardiovasc. Drugs Ther. 28 (2014) 281–289.

[15] E.M. Roth, M.R. Taskinen, H.N. Ginsberg, J.J. Kastelein, H.M. Colhoun, J.G. Robinson, et al., Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial, Int. J. Cardiol. 176 (2014) 55–61.

[16] D. Gaudet, D.J. Kereiakes, J.M. McKenney, E.M. Roth, C. Hanotin, D. Gipe, et al., Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials), Am. J. Cardiol. 114 (2014) 711–715.

[17] H.A. Deshmukh, H.M. Colhoun, T. Johnson, P.M. McKeigue, D.J. Betteridge, P.N. Durrington, et al., Genome-wide association study of genetic determinants of LDL-c response to atorvastatin therapy: importance of Lp(a), J. Lipid Res. 53 (2012) 1000–1011.

[18] P.M. Moriarty, P.D. Thompson, C.P. Cannon, J.R. Guyton, J. Bergeron, F.J. Zieve, et al., Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial, J. Clin. Lipidol. 9 (2015) 758–769.

[19] G. Hess, C. Chang, K. Chung, Lipid attainment among patients newly treated with lipid-altering drugs, Curr. Med. Res. Opin. 30 (2014) 1743–1756.

[20] C.P. Cannon, M.A. Blazing, R.P. Giugliano, A. McCagg, J.A. White, P. Theroux, et al., Ezetimibe added to statin therapy after acute coronary syndromes, N. Engl. J. Med. 372 (2015) 2387–2397.

[21] C.P. Cannon, E. Braunwald, C.H. McCabe, D.J. Rader, J.L. Rouleau, R. Belder, et al., Intensive versus moderate lipid lowering with statins after acute coronary syndromes, N. Engl. J. Med. 350 (2004) 1495–1504.

[22] J.C. LaRosa, S.M. Grundy, D.D. Waters, S. Shear, P. Barter, J.C. Fruchart, et al., Intensive lipid lowering with atorvastatin in patients with stable coronary disease, N. Engl. J. Med. 352 (2005) 1425–1435.

[23] G.G. Schwartz, L. Bessac, L.G. Berdan, D.L. Bhatt, V. Bittner, R. Diaz, et al., Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial, Am. Heart J. 168 (2014) 682–689.